

REVIEWS

HOW MUCH DO WE KNOW ABOUT THE ROLE OF VITAMIN D IN THE PATHOGENESIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Vitamin D is an essential steroid hormone. The role of Vitamin D in mineral metabolism and skeletal health as related to calcium homeostasis is well established. In addition to this role, vitamin D has been recently accepted also as immune modulator and thus it could be possibly implicated in the pathogenesis of systemic lupus erythematosus (SLE). This review focuses on the question: „Is vitamin D deficiency involved in the pathogenesis of SLE or is it a consequence of the disease state?” and comments the known positive effects of vitamin D supplementation on SLE disease activity.

Keywords: vitamin D, systemic lupus erythematosus (SLE)

INTRODUCTION

Vitamin D is a liposoluble steroid hormone formed by cyclopentane perhydro-phenanthrene ring system. Two physiological active forms exist in nature, 1,25-dihydroxyergocalciferol ($1,25(\text{OH})_2\text{D}_2$) and 1,25-dihydroxycholecalciferol ($1,25(\text{OH})_2\text{D}_3$). $1,25(\text{OH})_2\text{D}_3$ is the active form that is synthesized in humans and it is more effective than $1,25(\text{OH})_2\text{D}_2$ (20). The organs involved in vitamin D synthesis are skin, liver and kidney (18). Vitamin D synthesis begins in the skin where UVB brakes down C9-C10 bond of the precursor 7-dehydrocholesterol produc-

ing cholecalciferol. Cholecalciferol is transported to the liver and submitted to hydroxylation by 25-hydroxylase enzyme, forming 25-hydroxycholecalciferol ($25(\text{OH})\text{D}_3$). The final phase of the biosynthesis is in kidney where the enzyme 1- α -hydroxylase adds -OH group to position one and forms the active form $1,25(\text{OH})_2\text{D}_3$. Vitamin D is also obtained from some foods that contain ergocalciferol (D_2) or cholecalciferol (D_3), for example cod liver oil, fishes, eggs, mushrooms, etc.

The predominant form in blood is $25(\text{OH})\text{D}_3$, with ratio $1,25(\text{OH})_2\text{D}_3:25(\text{OH})\text{D}_3$ equal to 1:1000. The classical role of Vitamin D is assumed to be its effect on mineral metabolism and skeletal health as related to calcium homeostasis. The regulation of calcium uptake is due to the absorption at intestinal, bone and kidney levels (29). Recent studies discovered that calcitriol played an important role in what is called non-classical vitamin D functions that included cell apoptosis/anti-proliferation, providing anticancer effects and immunomodulation (21). The non-classical vitamin D functions are mediated by the vitamin D receptor (VDR) localized inside the cells of most tissues. $1,25(\text{OH})_2\text{D}_3$ binds with VDR and the

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complex $1,25(\text{OH})_2\text{D}_3$ -VDR with retinoid X receptor (RXRs) binds to the VDRE response elements on DNA changing the activity of different genes responsible for immunomodulation and regulation of various immunemediated processes (27).

In the current review, we aim to describe the immune modulatory effects of vitamin D, risk factors for vitamin D deficiency in patients with systemic lupus erythematosus (SLE), role of deficiency in pathogenesis of SLE, and potential positive effects of vitamin D supplementation on SLE disease activity.

VITAMIN D IMMUNE MODULATORY EFFECTS

The identification that the dendritic cells, which have central role to the maintenance of self-tolerance, can produce the biologically active form of vitamin D – $1,25(\text{OH})_2\text{D}_3$ and respond to this through the VDR in autocrine way suggests that vitamin D is an immune modulator (17,25,43). VDRs are found also in monocytes, macrophages and activated T and B cells and these cells also may convert vitamin D into its active form (45).

Vitamin D as immune modulator decreases Th1 CD4+ T cells and reduces the expression of IL-2, IFN- γ , TNF- α , IL-12, IL-6 and IL-17 (23,36,30); increases the production of IL-4, IL-5, and IL-10, leading to the development of a Th2 T-cell population (11, 30); increases the number and function of regulatory T cells (Treg) (51); inhibits Th17 cells important in the development of autoimmunity (23,36); inhibits monocyte differentiation into dendritic cells and blocks the stimulatory effects of T cells on them (8, 40); enhances monocyte differentiation into macrophages, but reduces their capacity to present antigens to lymphocytes by decreasing the expression of MHC-II molecule (15,31); prevents the proliferation of activated B cells and immunoglobulin production (26,46); induces apoptosis in activated B cells (16,55); inhibits posts switch memory B cells (16,45,55); inhibits production of IFN- γ from natural killer (NK) and T cells (60) (Figure 1).

The overall effect of $1,25(\text{OH})_2\text{D}_3$ is enhancement of the innate immune responses, while maintaining self-tolerance by inhibiting the adaptive immune responses. Over recent years it has been demonstrated that deficiency of $25(\text{OH})\text{D}_3$ is related to increasing risk of autoimmune diseases such as in-

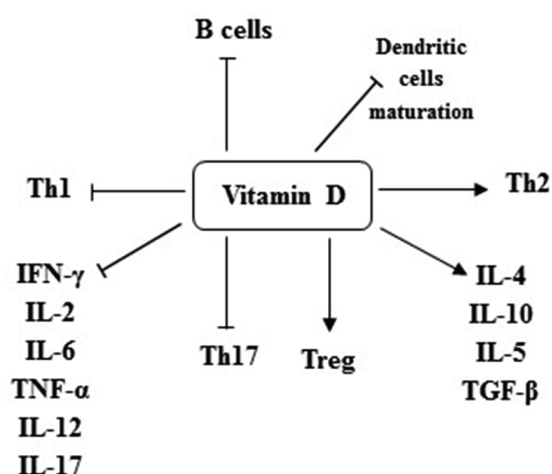


Figure 1. Vitamin D effects on the innate and adaptive immune response

sulin-dependent diabetes mellitus (IDDM), multiple sclerosis (MS), inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) (36).

SYSTEMIC LUPUS ERYTHEMATOSUS ACTIVITY AND VITAMIN D LEVELS

SLE is multiorgan autoimmune disease, more prevalent in African-Americans than in Caucasians, typically involving women in childbearing age (13). SLE is characterized by the loss of tolerance to nuclear antigens, immune complexes (ICs) depositions in tissues, delayed clearance of apoptotic cells and inflammatory cytokine release.

In many cohort studies, involving a large number of participants, low serum concentrations of $25(\text{OH})\text{D}_3$ correlated with SLE disease activity, assessed by SLEDAI (systemic lupus erythematosus disease activity index) and BILAG (British Isles Lupus Assessment Group) (3,6,7,10,12,19,24,35,38, 39,44,51,56,57,58,59). High titres of anti-double stranded (ds) DNA, anti-C1q antibodies and low serum levels of C3 and C4 complement are also useful tools to monitor SLE disease activity in practice. Also, significant inverse association between vitamin D levels and anti-dsDNA antibodies and direct association between vitamin D and complement C3 and C4 levels were established in several studies (9,10,35,37,51).

This significant inverse relation between vitamin D content and the determined SLE disease activity set an open question: Is vitamin D deficiency

involved in the pathogenesis of SLE or is it a consequence of the disease state? On one side, for SLE patients there are several risk factors for developing of 25(OH)D₃ deficiency:

1. One of most common disease manifestations is skin photosensitivity. Patients with SLE have to avoid sun exposure because of triggering of lupus flare. The result in blocking UVB-induced synthesis of cholecalciferol in the skin. It is known that people with darker skin pigmentation who are living far from the equator are especially prone to vitamin D deficiency, due to the protection of melanin from harmful UVB light. This could explain, in part, the vitamin D deficiency among African-Americans (25). It is no coincidence that this ethnic group has a higher risk for development of SLE and SLE is characterized by the most severe disease manifestations.
2. Chronic treatment of SLE patients with corticosteroids and anticonvulsants may alter the vitamin D metabolism, may reduce vitamin D-binding protein levels or downregulate the function of VDR (36,58).
3. Renal involvement in SLE patients with lupus nephritis may affect the hydroxylation step of 25(OH)D₃ in the kidneys (47).

On the other side, immune modulatory effects of vitamin D suggest possible major specific role in SLE pathogenesis. Ritterhouse et al. (2011) found evidences in this aspect, observing that vitamin D deficiency in healthy individuals was associated with an increased presence of antinuclear antibodies antibodies (ANA) (45). This finding is interesting, because it demonstrates the relation between vitamin D deficiency and the immune response in the absence of any other risk factors for vitamin D deficiency, typical for SLE patients, and suggests that vitamin D deficiency in autoimmunity is not solely a consequence of the disease. Also the fact that both healthy individuals and patients with SLE, positive for ANA, have decreased vitamin D suggests that vitamin D deficiency is involved in the early stages of SLE pathogenesis. Most studies have found a reduction in Treg cells in lupus patients in steroid therapy (14).

The role of vitamin D deficiency in the pathogenesis of SLE is also shown in other studies of Ritterhouse et al. (2011) – vitamin D deficiency is associated with significant hyperactivation of B cells, autoantibody production and IFN- α activity in SLE patients (45). IFN- α is one of the key cytokines in the pathogenesis of SLE. Association between raised IFN- α levels and increased disease activity in SLE is known fact. The complement system plays a major and complex role in the SLE, because it may prevent and also exacerbate the disease. Sakem et al. (2003) found that low levels of 25(OH)D₃ were directly related to the levels of IgG2 and complement component C4. In contrast these low levels of 25(OH)D₃ were reversely associated with the levels of IgG1 and IgA and complement component C3 (49). This shows that vitamin D insufficiency may lead to a poor immune response. Interestingly Linker-Israeli et. al. (2001) found increased numbers of T, B and NK cells expressing the VDR in SLE patients compared to healthy controls. This suggests that in SLE the immune system may have increased sensitivity to vitamin D (33).

VITAMIN D STATUS AND METHODS FOR ANALYSIS

According to The Institute of Medicine (IOM) and the Endocrine Society's Clinical Guidelines (22). Evaluation treatment and prevention of vitamin D deficiency, the optimum values for 25(OH)D₃ are at less or higher than 30 ng/ml because it is suggested that the maximum effect of vitamin D on calcium metabolism and bone health are in the interval between 30-40 ng/ml. Concentrations between 21-29 ng/ml are related to vitamin D insufficiency and values lower than 20 ng/ml (50 nmol/l) are considered vitamin D deficient because at this concentrations of 25(OH)D₃ parathormone (PTH) starts increasing.

The most important methods to determine the concentration of 25(OH)D₃ are immunoassays and chromatographic technics. Immunoassay methods are based on using a monoclonal antibody to 25(OH)D₃ with a colour product formation proportional to its concentration (enzyme-immunoassay, chemiluminescence) or using RIA method. Chromatographic methods (HPLC, LC-MS/MS), are separative technics that isolate and quantify the 25(OH)D₃ using mass-spectrometry. The advantages of immu-

noassay methods are that they have relatively short technological time, they are easy to manage and are not so expensive, but serum matrix can affect the results for 25(OH)D₃ concentrations. Chromatographic technics are referential methods with a high precision and accuracy, where the matrix cannot change the final results. However, they are very expensive, require long technological time and appropriate specific devices. Most studies reporting vitamin D levels use immunoassay methods that are not so accurate and precise as compared to chromatographic ones. This may be the cause for statistical errors and probably may explain why there are research groups that have not found an association between SLE disease activity and vitamin D status (28,34,47,48,50,53,54).

VITAMIN D SUPPLEMENTATION IN SLE PATIENTS

An interesting question, which is yet to be answered, is whether supplementation with vitamin D alters the course and prognosis of SLE. Interventional studies give contradictory results for the clinical outcomes. Three clinical studies showed no significant correlations between vitamin D supplementation and SLE disease activity (4,5,48). Other recent studies have found that supplementation with vitamin D is associated: with a decrease in disease activity (32,41) and in proteinuria (41); with an improvement in inflammatory and hemostatic parameters (1); with an increase in Treg cells and a reduction in Th1 and Th17 cells in a time dependent manner (11,42,52); with an inhibition of B cell proliferation, induction of apoptosis and reduced differentiation into plasma cells (16); with a decrease in memory B cells and in anti-DNA antibodies (52).

Despite established potential beneficial effects of vitamin D in SLE, to date, vitamin D supplementation is not the standard of care for patients with SLE because there is no consensus about recommended targeted vitamin D serum levels and the optimal mode and dose of vitamin D supplementation (23). Randomized, controlled trials are needed to evaluate the type, dose, duration and any side effects of the vitamin D supplementation needed to achieve pharmacological and clinical efficacy.

CONCLUSION

There are unresolved questions which answers will enucleate better the causal connection between

the levels of vitamin D and the pathogenesis of SLE: Which is the most appropriate phase of SLE to assess vitamin D levels (at the time of diagnosis or in remission)?; What is the cut off value of “normal” versus “insufficient” and “deficient” vitamin D levels in SLE patients?; What are the minimal beneficial levels of vitamin D in the management of SLE?; What should be the dose and duration of vitamin D supplementation?; How important are the intake of other medications, age, gender, geographic location, ethnicity, sun protective behaviour and genetic variations for the metabolism of vitamin D in SLE patients?

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